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GWAS Fertility Phenotypes

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Motivation for fertility GWAS

- evidence genetic component to biological fecundity (menopause, menarche) (Stolk et al. 2009; He et al. 2009)
- heritability age at first birth (twin-design) & number of children ~40% (Kohler et al. 1999)
- no research on genetic influences on reproductive choice
- fertility widely measured, highly harmonized, comparable traits

Trait definitions

Number of children ever born (NEB)

- continuous measure
- example of question:
  - *How many children have you given birth to?*
  - Often possible to distinguish between biological, adopted or step-children
  - Several cohorts only asked of women

Age at first birth (AFB)

- continuous measure
- example of question:
  - *How old were you when you had your first child?*
  - *What is the date of birth of your first child?*

Sample inclusion criteria

Number of children ever born (NEB)

a. Assessed for NEB at or after age 45 for women, age 55 for men

b. have given birth to a child (parous) and who have not (nulliparous);

Age at first birth (AFB)

a. Assessed for AFB and have given birth to a child (parous);

For both NEB & AFB:

- European ancestry;
- All relevant covariates are available for the individual;
- successfully genotyped genome-wide (recommended individual genotyping rate >95%)
- passed the cohort-specific standard quality controls, e.g., excluding individuals who are genetic outliers in the cohort.

Models

NEB / AFB: (OLS) regression for men

NEB / AFB: (OLS) regression for women

Family-based studies:

NEB / AFB: (OLS) regression for pooled sample

Covariates:

- The **number of reference alleles of each SNP**;
- Additional covariates necessary to **control for population stratification**, for example ancestry principle components. (Price *et al*., 2006) ;
- **Birth year of the cohort member**, represented by: [(birth year – 1900)/10], [(birth year – 1900)/10]^2 and [(birth year – 1900)/10]^3 to control for non-linear birth cohort effects.
- **Extra study specific covariates** such as discrete site indicator variables included if appropriate.

Current progress

- Analysis plan distributed April 2012
- Deadline uploading:
  - descriptives May 2012
  - GWAS results June 2012
- Future work: Quality control

Current progress (May 15 2012)

Total cohorts:

STATUS	N	%
contacted	162	
confirmed participation	45	27.8
confirmed NOT participating	42	25.9
in replication sample	9	5.6
sent reminder	66	40.7

Estimated sample size: ~100,000+

Meta-analysis

- **Analysts**
  - Nicola Barban & Jornt Mandemakers (Sociology, University of Groningen)
  - Ilja Nolte (Unit of Genetic Epidemiology & Bioinformatics, University Medical Center Groningen)
  - Niels Rietveld (Economics, University of Rotterdam)
- **Methodological advisor**: Harold Snieder (Unit of Genetic Epidemiology & Bioinformatics, University Medical Center Groningen)
- **Quality control**: Barban, Mandemakers & Nolte

Questions, discussion

- Additive allelic effect may be small even with large N

- Potential follow-up study:
  - go beyond additive GWAS models, to run **dominant models**
  - **estimate polygenic heritability** (Yang et al 2011; So et al. 2011); use GCTA (Yang et al. 2010/Nat Gen) – but requires raw data – possible?